U.S. POSTAGE
02

CLINICAL PROCEEDINGS

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

March 1952

VOLUME VIII NUMBER 3

So inviting in flavor, color and aroma...

MULCIN

puts a smile in the vitamin spoon

Vitamin time becomes a happy time when young patients see Mulcin coming! The refreshing orange flavor, pleasant aroma and sunny yellow color of this vitamin emulsion bring smiles to their faces. Mulcin's texture is smooth and light, with no trace of stickiness. Pouring is easy. Stable at room temperature, Mulcin needs no refrigeration. Children like taking Mulcin directly from the spoon. For infants, Mulcin may be mixed with formula, fruit juice or water.

A product of true pharmaceutical elegance and maximum acceptability, Mulcin is a distinguished member of Mead's vitamin family.

EACH TEASPOON OF MULCIN SUPPLIES:

Vitamin A	3000 units
Vitamin D	1000 units
Thiamine	1.0 mg.
Riboflavin	1.2 mg.
Niacinamide	8.0 mg.
Ascorbic Acid	50 mg.

Available in 4 oz. and economical 1 pint bottles.

MEAD'S

MEAD JOHNSON & CO.
EVANSVILLE 21, IND., U. S. A.

An achievement in pharmaceutical elegance

CLINICAL PROCEEDINGS

OF THE CHILDRENS HOSPITAL

13th and W Streets, Washington 9, D. C.

Vol. VIII *March 1952* No. 3

CONTENTS

BRONCHIECTASIS IN CHILDREN. *Marshall C. Sanford, M.D.* 43

MUCOVISCIDOSIS (FIBROCYSTIC DISEASE OF THE PANCREAS). *Joseph M. LoPresti, M.D.* 48

CARDIAC GLYCOGENOSIS. *Joseph McGovern, M.D.; Ruth Lau, M.D.; Francis J. Mastrota, M.D., and Samuel P. Bessman, M.D.* 57

CLINICO-PATHOLOGICAL CONFERENCE. *Ruth Lau, M.D; William Dorrance, and E. Clarence Rice, M.D.* 63

EDITOR-IN-CHIEF

E. CLARENCE RICE, M.D.

MANAGING EDITORS

FREDERIC G. BURKE, M.D. SIDNEY ROSS, M.D.

JOSEPH M. LOPRESTI, M.D.

ASSOCIATE EDITORS

GORDON W. DAISLEY, JR., M.D. JOHN P. MCGOVERN, M.D.

ADRIAN RECINOS, JR., M.D. MARSHALL C. SANFORD, M.D.

GENERAL MANAGER

JEANNE DECHANTAL RODDY

Contributing Editors from the Resident Staff: WILLIAM L. DORRANCE, M.D., FRANCIS MASTROTA, M.D., ROBERT H. PARROTT, M.D., HUBERT L. REID, M.D., AND EDWIN C. SHEPHERD, M.D.

Publications Committee of the Medical Staff: E. CLARENCE RICE, M.D., THOMAS BRADLEY, M.D., WILLIAM A. HOWARD, M.D., FREDERIC G. BURKE, M.D., AND SIDNEY ROSS, M.D.

PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinico-pathological conferences held every other Tuesday afternoon at 1:00 P.M., and from the monthly Staff meetings.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

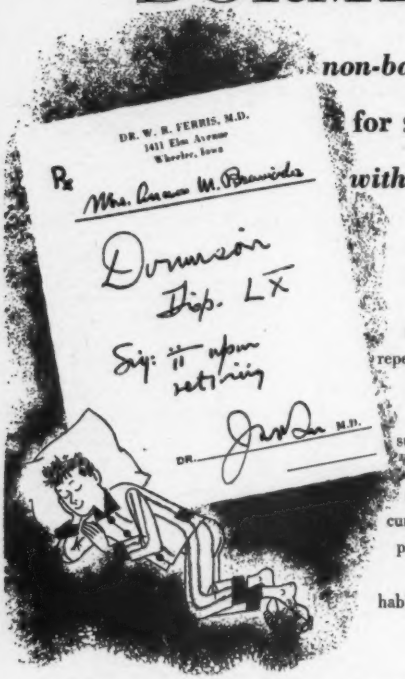
Subscription rate is $2.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D. C. Please notify on change of address.

Copyright 1952, Children's Hospital

Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

For insomnia... *you can prescribe with safety*

DORMISON



***non-barbiturate* hypnotic**

for SAFE, SOUND SLEEP

without drug hangover

The extraordinarily wide margin of safety of DORMISON permits patients who awaken in the early morning and desire more sleep to repeat the dose. DORMISON is rapidly metabolized (one to two hours) so that there is no prolonged suppressive action. Patients awaken rested and refreshed as from normal slumber. DORMISON has no cumulative effect, no toxic effects on prolonged use. There is no evidence to date that DORMISON has habit-forming or addiction properties.

DOSAGE: Two 250 mg. capsules are recommended, although many patients respond to one.

DORMISON* (methylparafynol-Schering), capsules of 250 mg., bottles of 100.

*T.M.

Schering **CORPORATION,** BLOOMFIELD, N. J.

DORMISON

BRONCHIECTASIS IN CHILDREN

Special Report No. 225

Marshall C. Sanford, M.D.

Bronchiectasis is one of the most common causes of chronic cough in children. It probably represents about 5 per cent of all the diseases occurring in infancy and childhood.[5] It is a chronic progressive disease which affects both sexes equally. Yet, it is frequently overlooked, misdiagnosed, and improperly treated.

While it may affect persons of any age, it characteristically begins in childhood or early adult life. It has been estimated that at least three-fourths of all cases of bronchiectasis originate during infancy or childhood. Oschner et al[7] in an analysis of 96 cases of bronchiectasis, found the onset occurred before the age of ten years in almost 50 per cent of these cases, and symptoms began during the first two years of life in 21 per cent. Field, in a report of 160 cases of bronchiectasis,[1,2,3] found that the onset of symptoms dated back to the first year of life in about 20 per cent of the cases.

The record room of most hospitals and the files of many a physician's office contain numerous such cases conveniently labelled "chronic bronchitis." Persistence of symptoms necessitating numerous visits all too frequently fail to spur an investigation into the etiology. Patients often outgrow the pediatric age range before advanced bronchiectasis becomes apparent, and many pediatricians fail to realize the later, disastrous damage caused by their failure to institute therapy. Studies of those patients, who in the pediatric age group were diagnosed as "chronic bronchitis" or "recurrent pneumonia," reveal that many of them do have established bronchiectasis.

Until bronchography has ruled out bronchiectasis, the diagnosis of chronic bronchitis should never be made. Early recognition and adequate therapy are mandatory because of the progressive nature of the disease. *In established bronchiectasis, surgical extirpation of the diseased pulmonary tissue is the only successful treatment.*

ETIOLOGY

This important chronic pulmonary disease, characterized by persistent cough and dilatation of a portion of the bronchial tree, was first described by Laennec in 1819. Until 1922, when iodized oil was introduced to outline the bronchial tree, the diagnosis was usually made at autopsy. The dilatation is thought to result when primary bronchitis is followed by atelectasis. Ulceration of the bronchial mucosa causes increased and abnormal secre-

tions which may block the bronchi and cause collapse of the adjacent lung tissue. In early stages, these changes may be reversible. Later, as a result of destruction of the contractile tissues and their replacement by fibrous tissue, these dilatations become irreversible. These factors are readily developed in infancy because the bronchi are small; and the expulsive efforts, weak.

Reversible or "pseudo bronchiectasis" refers to the dilatations which, with proper management, may return to normal. In the diagnosis of irreversibility, the knowledge of the duration, extent, and contour of the dilatation is most helpful.

Chronic sinusitis is frequently associated with bronchiectasis, but its role in the etiology has not been established. The triad of Kartagener with its bronchiectasis, chronic sinusitis, and situs inversus is well recognized, but is poorly understood.

DIAGNOSIS

The diagnosis of bronchiectasis is simple. Bronchography locates the area of pathology precisely. No single sign or symptom is pathognomonic; rather a clinical syndrome suggests the diagnosis. The syndrome consists of chronic cough, excessive secretions, and frequent bouts of and apparent increased susceptibility to upper respiratory infections in a child who, otherwise, may seem quite well.

The apparent paradox of severe symptoms with minimal physical and x-ray findings should always suggest this condition. In most cases, the symptoms date from childhood and, characteristically, follow an attack of pertussis, pneumonia, or measles. Although bronchography is necessary to confirm the diagnosis and to determine the exact extent of the disease process, the history suggests those patients in whom such studies are indicated.

Cough and expectoration may persist from the onset of disease. However, in many cases, these symptoms may disappear for a while and become prominent only after repeated attacks of bronchitis or bronchopneumonia. Even at this stage there may be long intervals of remission, especially during dry summer months, when symptoms are minimal. The number and severity of colds are likely to increase each winter.

SIGNS

A. *Physical Examination* is usually disarmingly unrevealing. The patient may appear remarkably well unless the case is most advanced. Signs of sepsis are often minimal or absent. Pulmonary physical findings often are limited to a few moist rales in the involved area or may be normal even with extensive involvement. Rales are the most important finding, and, if local-

ized, are significant; if generalized, however, they may signify bronchitis or asthma. Rales are best heard following a cough.

Some of these patients are underweight or underdeveloped. Failure to gain or actual weight loss may be one of the few suggestive findings. Postural defects are common. Typically, the shoulders are rounded; the spine, lordotic; and the abdomen, protuberant. Chest wall deformity, such as pigeon breast with lateral grooving, is a frequent finding. Clubbing of the fingers is diagnostic of irreversible bronchial changes, but is present only in the most advanced cases, and it seems to be related to the severity of the disease rather than to its extent or duration. Cyanosis and dyspnea occur as late manifestations in the most advanced cases.

B. *X-ray Examinations:* 1. Routine x-ray of the chest is often interpretated as normal. Increased bronchovascular markings, atelectatic areas, or cystic changes may be detected, but plain x-rays are never diagnostic of bronchiectasis and must be considered inconclusive unless confirmed by bronchogram.

2. Bronchography is the only definite means of establishing the diagnosis of bronchiectasis. The technique is simple, and when properly performed, the hazards are minimal. The reluctance of many physicians to obtain bronchograms on children under three years of age is no longer justified. Bronchography determines the type and extent of the disease. This information is essential in deciding the course of treatment. If surgical intervention is necessary, it shows the location and extent of lung to be resected. Therefore, the importance of complete and accurate bronchograms cannot be overemphasized.

Bronchograms are obtained by instilling a radio-opaque iodized oil into the lower pharynx or trachea followed by fluoroscopy and x-rays. As the material is introduced into the trachea, its course may be observed by fluoroscopy. The child's position may be altered in order to obtain complete filling of all lobes. Anteroposterior and oblique views allow visualization of all portions of the major bronchi.

Local anesthesia is satisfactory in most cases, but general anesthesia may be required for infants or the extremely uncooperative child. Bronchograms should not be performed immediately after a pulmonary infection because reversible dilatations are seen at this time and may be mistaken for true bronchiectasis. One should delay this study for two to three weeks following an attack of acute bronchitis and from four to six weeks following an attack of pneumonia.

The pulmonary segments most commonly involved are the lower lobes because there, gravity prohibits proper drainage of the secretions. The lingula is rarely, if ever, the only lobe involved.

C. *Bronchoscopy* is only a confirmatory measure in the establishment of

the diagnosis of bronchiectasis, but it is of considerable aid in the management of these cases both in the pre- and postoperative periods. It may be useful in evaluating the degree of mucous membrane erosion and the type and location of obstruction and in determining whether or not a foreign body is present. Bronchoscopic aspiration, prior to bronchography and postoperatively to remove retained secretions, is an established adjunct.

DIFFERENTIAL DIAGNOSIS

In establishing the diagnosis of bronchiectasis, the following conditions should be considered and excluded: recurrent acute bronchitis, chronic bronchitis, tuberculosis, pertussis, asthma, unresolved pneumonia, empyema, lung cyst, tumor, lung abscess, cystic fibrosis of the pancreas, and foreign body. Careful analysis of the history and physical examinations and x-ray findings will allow the exclusion of most of these.

PROGNOSIS

Excellent results are obtained in a high percentage of properly-selected and adequately-treated cases. Untreated bronchiectasis, however, is a serious, chronic and progressive disease. The serious implications of the untreated cough are dramatically emphasized when one realizes that most of the patients who develop bronchiectasis during the first ten years of life die before the age of forty.

SYMPTOMS

A. *Cough* is the cardinal symptom of bronchiectasis and is present in all cases. It may be constant or intermittent, varying with the type of child and the severity of the disease. The cough may disappear entirely during remissions, but becomes more severe after the next cold or attack of bronchitis. It may occur in paroxysms followed by periods of temporary relief. Often the cough has been present several months before medical aid is sought. It is most severe in the early morning as one attempts to empty the secretions which have pooled in the bronchi during the night.

B. *Sputum* is characteristically mucopurulent, thick, and somewhat stringy. It is foul only in the most advanced cases. Under the age of three years, children swallow their sputum and it is not until the child has reached his eighth year that he expectorates all or most of it. Obviously, the quantity of sputum varies greatly and a determination of the amount may be difficult. As the patient's position is altered, bronchial drainage is facilitated, resulting in increased production of sputum. The amount of sputum is not necessarily a good index of the extent of the disease. In the so-called dry bronchiectasis, sputum is scant or absent. As with cough, sputum production is greatest in the early morning.

C. *Hemoptysis*. While hemoptysis is common in adults, it is a rare occur-

rence in children, although it has been known to occur after the age of three years. Before this age, it may be present but since the sputum is swallowed, blood is not visible.

D. *Wheeze.* Partial bronchial obstruction produces a typical wheeze common in children, but rare in adults. The small size of the bronchi in the early stage of development undoubtedly accounts for the high incidence in pediatric patients.

TREATMENT

The type of treatment to be employed in each case depends on the severity of symptoms, the degree and extent of the disease, and the age and condition of the patient. Patients with minimal symptoms do not warrant surgical intervention. The more localized the process, the more amenable it is to surgical resection.

A. *Medical.* During the early stages, many cases of bronchiectasis are reversible and adequate therapy may revert slightly-damaged tissues to normal. Unfortunately, with the exception of these early cases, medical therapy is only palliative. The morbidity and mortality of cases subjected to medical treatment alone is high.

Preventive therapy is most useful when it includes immunization against pertussis, vigorous attempts to clear allergies and to prevent asthma, clearing of chronic sinusitis, and the removal of diseased tonsils and adenoids.

Medical therapy is a useful adjunct in preparing these patients for operation. Postural drainage, breathing exercises, expectorants, bronchoscopic aspiration, and antibiotic therapy are the most helpful adjuncts in the management of these cases. Although antibiotic therapy has been disappointing, it still plays a definite role in the therapy of these cases.

B. *Surgical.* The only successful treatment in established bronchiectasis is the surgical resection of the diseased pulmonary tissue. Pulmonary resection is a major operative procedure, but it is well tolerated by children and gives excellent results in a high percentage of properly-selected cases. The morbidity and mortality are minimal. Early surgical intervention obviates the hazards of this disease which would be faced in adult life if the condition were allowed to progress. In growing children, the remaining pulmonary tissue increases its functional activity following pulmonary resection. Careful observation and management are required in the early postoperative period. Tracheal and bronchoscopic aspirations sometimes are necessary.

REFERENCES

1. Field, C. E.: Bronchiectasis in Childhood, Pediatrics, (July) 1949.
2. Field, C. E.: Bronchiectasis in Childhood, Pediatrics, pp. 231 (August) 1949.

3. Field, C. E.: Bronchiectasis in Childhood, Pediatrics, pp. 355 (September) 1949.
4. Miller, J. B., Conyer, W. H., Jr., and Dinhoffer, N.: A Simple Safe Bronchographic Technique for Children, J. Peds. **36:** 6, 721 (June) 1950.
5. Dorner, R. A.: What the General Practitioner Should Know About Bronchiectasis. J. of Iowa Med. Soc. (July) 1950.
6. Buckles, M.: The Surgical Treatment of Bronchiectasis, J. A. M. A. **143:** 4, 344 (May 27) 1950.
7. Oschner, A., DeBakey, M., and DeCamp, P. T.: Bronchiectasis, its Curative Treatment by Pulmonary Resection, Surgery, Vol. 25, No. 4 (April) 1949.
8. Strieder, J. W.: The Surgical Aspects of Bronchiectasis, New Eng. J. Med. **238:** 109, 1948.

MUCOVISCIDOSIS

(FIBROCYSTIC DISEASE OF THE PANCREAS)*

Case Report No. 226

Joseph M. LoPresti, M.D.† D. J. G. 49-3192

The following case is reported as being typical of mucoviscidosis (fibrocystic disease of the pancreas) and to review for the medical practitioner this interesting and relatively frequent clinical entity.

CASE REPORT

D. J. G., a white female, was admitted to The Children's Hospital on March 8, 1949 at the age of three months. The chief complaints were diarrhea dating from birth and a failure to gain weight. The history revealed that the patient had a persistent diarrhea from the date of birth. The stools were mustard-colored, slimy, not mal-odorous, watery, and were passed about twelve times a day. The infant's appetite had been excellent, and she was breast-fed up until the time of admission. Her weight at birth was 6 pounds, 14 ounces; and, at the time of admission, 8 pounds, 4 ounces. At two and one-half months of age, the patient developed a cough productive of large amounts of white mucoid material. A diagnosis of bronchitis was made which responded to penicillin therapy. Shortly thereafter, coughing paroxysms occurred associated with vomiting. She was then hospitalized. Family history was noncontributory. Four siblings and the mother and father are all normal.

Physical examination on admission revealed a temperature of 101.0 F.; pulse, 140 per minute; and a respiratory rate of 60 per minute. The patient was pale, fully developed, and undernourished. Paroxysms of coughing were noted. Examination of the chest revealed decreased resonance, dullness, and rales in the left lower lung field

---

* This article was presented as a post-graduate lecture to the House Staff of The Children Hospital of the District of Columbia.

† Assistant Professor of Pediatrics, George Washington University, School of Medicine, Washington, D. C.

posteriorly. The laboratory examinations showed a secondary anemia and a pneumonic process in the left lower lung. The Shwachman X-ray film test for trypsin showed an absence of digestion of the gelatin. Duodenal drainage failed to reveal any trypsin in the fluid obtained.

The patient was placed on a high protein diet, pancreatin, vitamins, and penicillin therapy. The anemia was corrected with blood transfusions. The respiratory symptoms abated gradually. The diarrhea cleared, and the infant gained weight slowly. She was discharged on March 24, 1949 weighing 10 pounds, 14 ounces.

Since the first admission, the patient has been hospitalized on two separate occasions, at the ages of eight and eighteen months respectively. Both of these admissions were occasioned by bronchopneumonia and cyanosis. She responded dramatically during these admissions to the administration of aureomycin. At the time of the last discharge, June 12, 1950, she weighed 16 pounds; there was clubbing of the fingers and toes; the abdomen protruded; and the muscles were thin and flabby. The outlook for this patient is felt to be poor.

DISCUSSION

Introduction

Mucoviscidosis (fibrocystic disease of the pancreas) may be defined as a systemic disease in which an abnormally thick mucoviscid secretion is produced throughout many organ systems of the body. The pathological changes in the pancreas and lungs which secondarily are produced by this abnormal secretion are responsible for the characteristic clinical features. The most prominent physiologic change is a pancreatic insufficiency with consequent poor digestion and utilization of protein, fat, and fat-soluble vitamins. The clinical characteristics are an early onset; a failure to gain weight on a normal diet; an excellent appetite; the presence of large, foul stools; and the development of chronic bronchitis, bronchopneumonia, and often of bronchiectasis.

Mucoviscidosis appears to be a congenital and familial disease and its incidence has been estimated at approximately 2 per 1000 live births.

History

A brief historical review reveals that the knowledge of this disease entity is fairly recent. In 1905, Landsteiner[1] recorded the earliest pathological description of the pancreatic lesion. Garrod and Hurtley[2] reported the first careful clinical observations in 1913; and in 1919, Passini[3] associated the congenital intestinal anomaly with the pancreatic lesion. It was not until 1932 that Siwe[4] confirmed the clinical diagnosis by an actual examination of the duodenal juice for pancreatic enzymes. Andersen[5] in 1938, classified patients with mucoviscidosis into three clinical categories. In 1944, on the basis of careful pathological studies, Farber[6] demonstrated the systemic nature of the disease and suggested the term "mucoviscidosis." Finally, in 1951, Shwachman[7] indicated that the earliest change in the duodenal juice of patients with mucoviscidosis may be an increase in its viscosity with no significant alteration in the trypsin content.

Etiology

The exact etiology of fibrocystic disease is as yet undetermined and the basic defect responsible for the production of the abnormal mucoviscid secretion is unknown. The familial nature of the disease is affirmed by the fact that it occurs in approximately one-fourth of the siblings in affected families and may be present in one or both of twins. There is no predilection for either sex and mucoviscidosis has been reported in almost all races with the exception of the oriental in which the condition is apparently rare. Its congenital nature is attested to by the group of patients who are born with the pancreatic lesion and who have clinical symptoms dating from birth (meconium ileus).

Pathology

The pathology of mucoviscidosis is protean. In the pancreas the changes appear to be secondary to obstruction of the large and small ducts by an abnormal secretion. This mucoviscid substance takes up the eosinophilic stain. The smaller ducts and acini are dilated in varying degrees and contain eosinophilic concretions. The epithelial cells lining the ducts and acini are flattened in proportion to the dilatation. Within and between the lobules there is a proliferation of fibrous tissue often with a scattered infiltration of lymphocytes. In late cases there may be an actual reduction in the number of acini, some of the concretions may be calcified, and fatty infiltration may be present. The careful pathological investigations of Farber[6] have demonstrated the systemic nature of the basic lesion. Changes similar to those in the pancreas and evidence of an abnormal secretion are present in the lungs, the intestinal tract, the salivary glands, and elsewhere. These findings have suggested the term "mucoviscidosis" as a proper designation for this disease entity. The pathological changes in the lungs are constant. The most prominent finding is a chronic bronchitis in which the bronchial walls are greatly thickened with fibrous tissue proliferation and extensive lymphocytic infiltration. In many instances a tubular bronchiectasis is found. Invariably, a superimposed acute suppurative process occurs and the bronchial tree is often filled with a thick, viscous, mucopurulent material from which *Hemolytic staphylococcus aureus* is most often cultured. Obstructive emphysema, scattered abscesses, or small areas of atelectasis may or may not be present. Vitamin A deficiency is evidenced in almost all cases by a characteristic squamous metaplasia of the epithelium lining the trachea, bronchi, and renal pelves. In some cases a frank xerophthalmia may be present. Almost all of the patients with mucoviscidosis have a hepatomegaly. On microscopic examination, the liver shows fatty infiltration. Whether this change is secondary to starvation or to the basic pathological defect is debatable.

Pathologic Physiology

An understanding of the pathologic physiology of mucoviscidosis is essential to a rational therapeutic approach to the disease. The pancreatic lesion with its attendant pancreatic insufficiency produces constant and definite effects on digestion. The pathology elsewhere alters the lungs and the intestinal tract. Protein is poorly digested and from 20 to 65 per cent of dietary protein is excreted in the feces. Despite this excessive loss, most of the patients have a normal serum protein level. This would indicate that some proteins or protein fractions are better utilized than others. On a normal diet, patients with mucoviscidosis will excrete from 30 to 60 per cent of the fat which is ingested with a concomitant loss of calories and fat-soluble essential substances. The fecal fat may appear as neutral fats or fatty acids, either free or combined as soaps. This latter finding is probably produced by the splitting of neutral fat by intestinal flora. The fat-soluble vitamins and essential substances are poorly utilized. The serum cholesterol level is usually low and vitamin A deficiency is frequently encountered. Vitamin A absorption curves are often flat and carotene, in particular, is not absorbed. The serum vitamin A level can be improved by the administration of massive oral doses of a concentrated preparation, but the low serum carotene levels will not be affected. Untreated cases of mucoviscidosis will develop hemorrhagic tendencies and a prolongation of the prothrombin time. These are correctible by the parenteral administration of vitamin K. The digestion of carbohydrates is little impaired in this disease and both sugars and starches are well-utilized and well-tolerated. There is an excessive loss of minerals in the feces. An important consideration is the deficiency in total calories produced by the pancreatic insufficiency. From 25 to 50 per cent of the caloric intake is lost in the feces. *Caloric loss is greater when the dietary fat is increased.*

The relationship of the respiratory infection to the nutritional difficulty is not clear. The position that it is related to the squamous metaplasia caused by vitamin A deficiency would appear to be untenable. If the serum vitamin A levels are restored, the respiratory changes progress unabated. Farber's[6] studies, which indicate that the disease is a systemic one and that the basic pathology in the lungs is similar to that in the pancreas would seem to be the more logical view. Shwachman[7] has recently reported a group of patients with mucoviscidosis who possess normal trypsin levels in the duodenal juice, but in whom the respiratory symptoms predominate. This report would support the view that the disease is a systemic one, and that the designation "pancreatic fibrosis of the pancreas" is a misleading one.

The pathological lesions which are sometimes observed in the digestive tract are further evidence of the systemic nature of mucoviscidosis. The intestinal mucosa may be thickened by fibrosis and infiltrated with lympho-

cytes. The extent to which these changes contribute to the impaired physiology is, as yet, undetermined.

Symptomatology

On the basis of clinical observations, Andersen[5] has categorized patients with mucoviscidosis into three main groups:

Group I includes a small number of new-borns with congenital intestinal obstruction secondary to a meconium ileus. The clinical features are those of a lower small bowel obstruction. These include the symptoms of vomiting (the vomitus contains bile and fecal material), abdominal distension, and the failure to pass meconium stools. The diagnosis may be suspected by the presence of the disease in a sibling and confirmed either by operation or, more frequently, at the autopsy table.

Group II includes those cases in whom there is an early onset of respiratory symptoms. A small number of these infants will have continuous or intermittent diarrhea in the neonatal period and frequently die in the first few months of life. By far the greatest number of patients with mucoviscidosis will be normal at birth and make satisfactory progress for a week to several months; then they will fail to gain weight despite an adequate diet and an excellent appetite. Invariably, frequent formula changes will have been made in an attempt to correct the difficulty. While there will be no increase in the number of bowel movements, the passage of foul stools will appear between birth and six months of life. Occasionally these infants will have brief episodes of diarrhea. Early in this period, frequent colds will make their appearance or the patient may develop one cold with a persistent hacking cough. The cough may be paroxysmal and associated with vomiting so that the diagnosis of pertussis will be entertained. In time, continuous hacking will occur, the cough will become ineffectual with occasional paroxysms, and cyanosis may appear abruptly. Death usually follows the appearance of cyanosis. Physical examination will reveal the celiac syndrome, i.e., a small infant with a distended abdomen, large trunk, and thin extremities. The eyelids will be mildly reddened and occasionally xerophthalmia will be noted. There will be a chronic purulent nasal discharge and otitis media will frequently be seen. The respiratory rate will be rapid; and respirations, labored. On percussion and auscultation of the lung fields, hyperresonance, bronchi, and coarse rales will be noted. Acrocyanosis and clubbing of the fingers and toes often will be present.

Group III is composed of another small number of patients who develop respiratory symptoms after six months of age. This group is the most difficult to diagnose. Characteristically, these cases have two to four large foul stools daily throughout life. They possess an excellent appetite and growth is only mildly retarded. The abdomen is large. There is usually a history of several attacks of bronchitis and one or two episodes of bron-

chopneumonia which had responded to treatment. Between the ages of one to four years, these children develop a chronic productive cough, weight loss, irritability, and cessation of growth. It is not unusual to note repeated rectal prolapse at this time. Within a year bronchopneumonia, cough, and cyanosis appear which will not respond to treatment. At this point the patients will present the distinctive appearance of the celiac syndrome (large trunk, thin extremities, and distended abdomen). In addition, there will be frequently a severe paroxysmal cough accompanied by cyanosis; and clubbing of the fingers and toes often will be present.

Kessler and Andersen[8] have recently reported that patients with mucoviscidosis appear to be peculiarly susceptible to heat prostration. It is suggested that in hot weather, the signs of marked dehydration, fever, and circulatory collapse in an infant or young child without apparent cause may be the first indication of the disease.

Several laboratory tests are of definite aid in establishing the diagnosis. On a normal diet, fat forms from 30 to 60 per cent of the dried weight of the stool. The fat may be largely in the form of neutral fat or of fatty acids, either free or combined as soaps. Microscopic examination of the feces will show an abundance of fat droplets.

A barium meal will reveal abnormal motility of the small bowel. There will be excessive segmentation of the barium with areas of spasm and dilatation of the intestine and the mucosal pattern will be coarsened or obliterated.

The only reliable method of establishing the diagnosis is to examine the duodenal juice. Shwachman[7] has indicated that some patients may show a normal trypsin content in the duodenal juice; however, the viscosity may be greatly increased when determined by the Ostwald viscometer. In most cases, tryptic activity will be absent or greatly reduced. Shwachman's x-ray film test for trypsin[9] is an ideal screening procedure for the office practitioner. It utilizes a small piece of exposed but undeveloped x-ray film and a fresh specimen of the patient's stool in varying saline dilutions. A positive test for trypsin is indicated by an area of gelatin digestion. False positive reactions occur due to bacterial digestion of the gelatin. However, under the age of one year the test is quite accurate and reliable. A recent modification of Shwachman's test renders it even more accurate.[10] It should be stressed that all suspected cases ultimately must be subjected to duodenal drainage and the duodenal juice analyzed for its viscosity and trypsin content.

The vitamin A absorption test will be flat; and the serum carotene level, always low in cases of mucoviscidosis. If a large dose of vitamin A concentrate is administered to one of these patients, the fasting blood serum will show a normal level of vitamin A, *but there will be little or no carotene found.*

A roentgenogram of the chest may frequently suggest the diagnosis.

Characteristically, it will reveal a diffuse peribronchial thickening with or without bronchiectasis. Small and persistent areas of atelectasis and emphysema may be present.

Diagnosis

The diagnosis of mucoviscidosis should be suspected in any infant or young child who possesses digestive symptoms associated with respiratory disease. It should be considered seriously in all cases of congenital intestinal obstruction. A family history of the disease may be elicited. All conditions must be considered in the differential diagnosis which produce the celiac syndrome. *The only reliable method of establishing the diagnosis is by direct examination and analysis of the duodenal juice.*

A subdural hematoma may produce malnutrition, vomiting, and the celiac syndrome. A history of a difficult, prolonged labor should suggest this possibility. Direct examination of the subdural fluid will establish the diagnosis.

Starvation will ultimately result in the celiac syndrome. However, the history of an inadequate dietary intake and a dramatic response to a proper diet along with the absence of respiratory symptoms will differentiate this likelihood.

Malrotation or stenosis of the intestine with resultant chronic or intermittent intestinal obstruction should be ruled out by barium meal and enema studies.

Tuberculosis and tuberculous peritonitis are characterized by a history of exposure, positive skin tests, and the finding of the causative organism in the gastric washings.

Chronic ulcerative colitis is encountered only rarely in pediatric practice. The proctoscopic examination and barium enema studies will establish the diagnosis.

Celiac disease should always be considered in the differential diagnosis. However, the exclusive features are a strong family history, intolerance to dietary starch, and a flat glucose tolerance curve. The duodenal juice will show a low amylase content and normal tryptic activity. Carotene absorption is unimpaired in celiac disease.

Other disease entities to be differentiated include epidemic diarrhea of the new-born, pertussis, asthma, lipoid pneumonia, congenital atelectasis, and bronchiectasis associated with chronic sinusitis and otitis media.

Treatment

The therapy of mucoviscidosis is predicated by an understanding of the pathologic physiology, and the sheet anchor in the management of these

patients is a proper diet. A secondary consideration is the control of respiratory infection. Surgical procedures, such as splanchnicectomy, appear to have little or no effect on the course of the disease.[11]

The basic diet of the patient with this disease should supply a high caloric, high protein and carbohydrate, and low fat intake. The caloric requirements in these patients is about 180 calories per kilogram of body weight per day. The protein intake should be double the normal. For the young infants, this amount should be 10 to 12 grams of protein per kilogram of body weight for each 24 hours; and in children after the age of two years, the protein requirements will be satisfied by 8 grams of protein per kilogram of body weight each day. In the younger infants, protein hydrolysate, 2 to 3 grams per kilogram of body weight may be added each day to a protein milk formula. The fat in the diet should be low but the essential food substances which are fat-soluble must be provided. These include vitamins A, D, and K; the essential fatty acids; and phospholipids. For the most part, the essential substances are contained in peanut butter and egg yolk which are well-tolerated. The carbohydrate content of the diet should be high. These patients utilize glucose, sucrose, and levulose very well. Fruits and vegetables have the added advantage of supplying vitamins and minerals.

Almost all of the patients with mucoviscidosis have pancreatic insufficiency. The addition of pancreatin, either in powdered or capsule form is a worthwhile measure. It improves the utilization of food, particularly in marasmic infants. In the older patients, 1 to 2 grams of pancreatin should be given with each meal, while in the young infants, 1 gram of pancreatin should be added to each 8 ounces of formula.

Vitamin supplements are important. Vitamin A levels will be normal when large doses of a concentrated preparation are administered orally. A daily dose of 20,000 to 40,000 units of concentrated cod liver oil is sufficient. Parenteral vitamin K (50 to 75 milligrams per day) should be given when the prothrombin time is prolonged. Other vitamins, e.g., the B-complex and vitamin C, are supplied orally.

The management of the respiratory symptoms in patients with mucoviscidosis poses a problem. Exposure to respiratory infections should be avoided. The routine administration of prophylactic doses of sulfadiazine may be instituted. When acute infection or suppurative bronchitis occur, the prompt use of specific therapy is mandatory. The usual etiologic agent of secondary infection in these patients is *Hemolytic staphylococcus aureus.* There seems to be little doubt that the drug of choice in staphylococcic infections is aureomycin.[12] The therapeutic dose lies in the range of 50 milligrams per kilogram of body weight per 24 hours, adminstered orally,

in a 4 or 6 hour divided dosage schedule. The prolonged use of the antibiotics may increase the opportunity for the emergence of resistant strains of organisms, e.g., *Pseudomonas aeruginosa*.[13]

Prognosis

Before the advent of antibiotic therapy and the increased knowledge of dietary requirements, the prognosis in mucoviscidosis was hopeless. Seventy-five per cent of the patients died before the first year of life and most of the remainder were dead before the age of 5 years. Early diagnosis and the institution of proper dietary measures before respiratory symptoms occur offers the best hope for these patients. Further evaluation of the improved prognosis must await the passage of time. If the respiratory symptoms occur in the first 2 or 3 months, the prognosis is still poor.

REFERENCES

1. Landsteiner, K.: Darvirschluss durch eingedicktes Meconium; Pankreatitis, Centralbl. f. allg. Path. u. path. Anat. **16:** 903, 1905.
2. Garrod, A. E. and Hurtley, W. H.: Congenital Family Steatorrhea, Quart. J. Med. **6:** 242, 1912–13.
3. Passini, F.: Pankreaserkrankung als Ursache des Nichtgedeihens von Kindern, Deutsche med. Wchnschr. **45:** 851, 1919.
4. Siwe, S.: Uber die exokrine Funktion des Pankreas und die exokrinan Teiles des Pankreas, Deutsches Arch. f. Klin, Med. **173:** 339, 1932.
5. Andersen, D. H.: Cystic fibrosis of the pancreas and its relation to celiac disease, a clinical and pathological study, Am. J. Dis. Child. **56:** 344, 1938.
6. Farber, S.: Pancreatic function and Disease in Early Life, V. Pathological Changes Associated with Pancreatic Insufficiency in Early Life, Arch. Path. **37:** 238, 1944.
7. Shwachman, H.: Progress in the Study of "Mucoviscidosis" (Pancreatic fibrosis), Peds. **6:** 153, 1951.
8. Kessler, W. R. and Andersen, D. H.: Heat Prostration in Fibrocystic Disease of the Pancreas and other Conditions, Peds. **8:** 648, 1951.
9. Shwachman, H., Patterson, P. R., and Laguna, J.: Studies in Pancreatic Fibrosis; Simple Diagnostic Gelatin Film Test for Stool Trypsin, Peds. **4:** 222, 1949.
10. Gaffney, P. C.: Source of Error in Test for Stool Trypsin, Peds. **8:** 82, 1951.
11. Ayers, W. B., Stowens, D., Ochsner, A., and Platou, R. U.: Splanchnicectomy for Pancreatic Fibrosis, Peds. **8:** 657, 1951.
12. Shwachman, H., Crocker, A. C., Foley, G. E., and Patterson, P. R.: Aureomycin Treatment in Pulmonary Involvement of Pancreatic Fibrosis, N. Eng. J. Med. **241:** 185, 1949.
13. Garrod, S. D., Richmond, J. B., and Hirsch, M. M.: Pseudomonas Aeruginosa Infection as a Complication of Therapy in Pancreatic Fibrosis, Peds. **8:** 482, 1951.

CARDIAC GLYCOGENOSIS

Case Report No. 227

Joseph McGovern, M.D.
Ruth Lau, M.D.
Francis J. Mastrota, M.D.
Samuel P. Bessman, M.D.

INTRODUCTION

Cardiac glycogenosis is considered to be quite rare[1, 2] and the possibility that glycogen storage may occur more frequently than suspected is suggested by the following case in which a fortuitous determination of cardiac glycogen at autopsy established the diagnosis.

CASE REPORT

J. R., a twenty month old male was brought to Children's Hospital on June 26, 1951 from a hospital in a neighboring state with the chief complaint of fatigue of two months' duration*. The patient was perfectly well until six months prior to admission when an episode of acute tonsillitis occurred which subsided with penicillin therapy. In the next four months there were four more attacks all apparently responding to penicillin. Two months prior to admission, it was seen that the patient no longer wanted to play, tired easily, and lost his appetite. One month prior to entry diagnostic studies at another hospital showed anemia, normal urinalysis, and increase in heart size by x-ray (Fig. 1). The treatment consisted of two whole blood transfusions of 200 milliliters each, iron, and vitamins. No improvement was seen during the next three weeks. One week prior to admission, the patient suddenly developed a fever and "swelling of the face and feet." Hospitalization at still another hospital revealed an acutely ill, malnourished white male, who was cyanotic and dyspneic. The pulse rate was 140 per minute; respiratory rate, 32 per minute; temperature, 102.0 F., and blood pressure, 90/?. There was a purulent drainage from the tonsils with anterior cervical adenopathy and moderate cervical venous distension. The right border of the heart was percussed ¾ of an inch to the right of the sternum and the left border at the anterior axillary line. The liver was firm and palpable below the right costal margin. Except for a moderate leukocytosis and the predominance of lymphocytes, the remainder of the hemogram including the sedimentation rate was normal. There was albuminuria, hematuria, and pyuria, and the blood urea nitrogen was elevated (170 milligrams per cent). Serum protein and A:G ratio were normal. An increase in the size of the heart shadow was demonstrable by x-ray. There was no evidence of pulmonary infiltration. Tuberculin tests and serologic test for syphilis were negative. After one week of study, the patient was transferred to Children's Hospital.

The admission temperature was 102.0 F.; pulse, 160; respirations, 80; and blood pressure, 130/80. The patient was pallid and listless. The point of maximum cardiac impulse was 6 centimeters from the midsternal line in the fifth interspace and the liver was palpable 6 centimeters below the right costal margin. The diagnosis at this time was cardiac decompensation secondary to nephritis.

* This patient was admitted to the private service of Dr. Frederic G. Burke.

Laboratory studies showed a leukocytosis of 12,000 with 70 per cent lymphocytes. The urine contained 800 milligrams per liter of albumin with occasional white blood cells and one-two hyaline casts per high power field. The carbon dioxide combining power was 43 volumes per cent. X-rays revealed pulmonary congestion, cardiac enlargement, enlarged liver, and generalized bony demineralization.

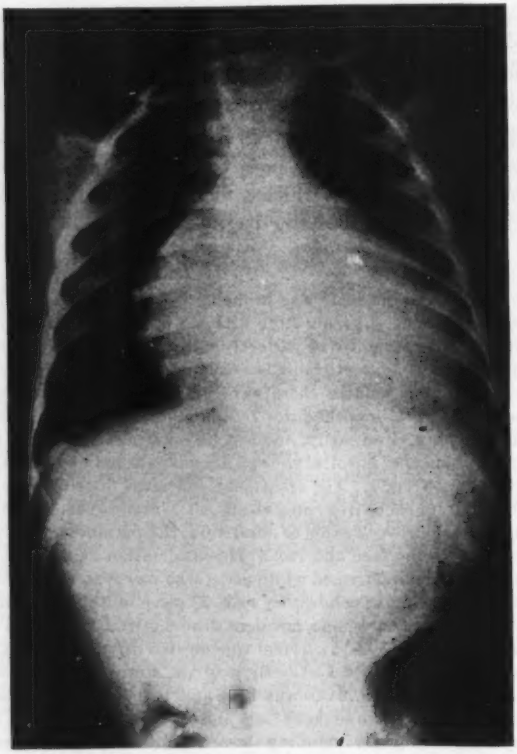


FIG. 1. X-ray of the chest taken on the first hospitalization day prior to the development of nephritis showing enlargement of the heart.

Within six days, the patient's decompensation improved under a regime of 15 drops of tincture of digitalis initially and maintenance dose of 5 drops daily; salt poor diet; and magnesium sulfate, 50 per cent, in 5 milliliter dosage intramuscularly for the first three days. X-ray of the chest showed the cardiomegaly to persist but the pulmonary congestion was no longer present. Intravenous pyelogram and repeat urinalyses were normal. The patient continued to improve clinically until the fourteenth hospital day when he suddenly developed cyanosis, tachycardia and hypertension—160/110. At this time the liver and spleen were both palpable. The prothrombin was 15 per cent of normal.

Serum cholesterol was 150 milligrams per 100 milliliters. Serum amylase was 12 units (normal 20 to 40). Fasting blood sugar was 105 milligrams per 100 milliliters. The non-protein nitrogen was 26 per cent. There was a relative lymphocytosis. Thymol turbidity was less than 1 unit and nose, throat, and urine cultures were negative. The patient improved spontaneously. On the twenty-third hospital day, the patient suddenly cried and began to vomit, cough, and have hyperpnea and tachycardia again. X-rays showed pulmonary congestion in addition to the enlarged heart. Fluoroscopy revealed no signs characteristic of congenital heart disease. Tincture of digitalis was increased to 15 drops daily and some immediate improvement was noted. During the ensuing two weeks there were four episodes in which the child suddenly cried out as though in pain, became pale, and assumed a knee-chest position. Attacks would last about 30 minutes and were associated with a weak rapid pulse and shallow

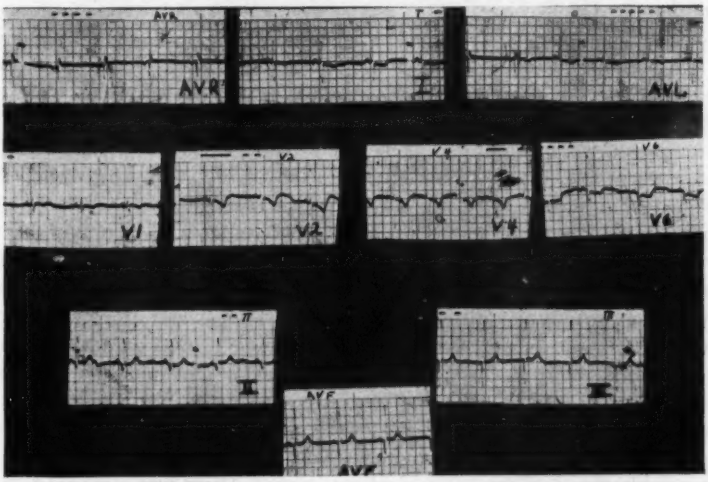


FIG. 2. Electrocardiogram taken shortly before the patient's death

rapid respirations. Morphine sulfate, 1 milligram per 10 pounds by vein and nasal oxygen were of some help during the acute episodes. Electrocardiogram was highly abnormal with inverted T waves in all chest leads, lead 1 and AVL (c.f. Fig. 2). There was no particular pattern observed. Bone marrow examination showed a moderate reduction in the number of megakaryocytes, an increase in the number of leukocytes, and an excess in the number of lymphocytes. Fasting blood sugar (Folini) was 60 milligrams per cent on two occasions. Glucose, insulin, and adrenalin tolerance tests were normal. Total eosinophile counts were slightly elevated, but good adrenal response was demonstrated by a sharp drop in the eosinophiles on the intramuscular administration of 10 milligrams of ACTH.

The patient's clinical condition deteriorated rapidly during the next ten days. The episodes of pallor and hyperpnea occurred almost daily and continuous oxygen was administered. Hypertension, tachypnea, tachycardia, and anorexia continued. Repeat fluoroscopy showed no change except that the pulsations of the pulmonary

artery were barely discernible. Supportive measures included a three-day course of corticotrophine (50 milligrams per day). The patient quietly expired on the forty-eighth hospital day while a muscle biopsy was being performed.

AUTOPSY FINDINGS

The remarkable findings were confined to the heart and lungs. The heart was enlarged to almost three times normal size occupying the majority of the anterior thorax. The auricles and ventricles were proportionally enlarged and the usual cardiac contour was not altered. The heart weighed 162 grams, (normal 55 grams). The atrial walls showed no changes. The ventricular walls were thickened, the right averaging 4 millimeters, the left 8 millimeters. The myocardium on cut section was firm and reddish tan with occasionally greyish-white stellate areas which were found most frequently in the region of the subendocardium. The endocardium of the left auricle and ventricle was thickened and opaque. The papillary muscles were enlarged and firm. The valve cusps and coronary vessels were normal. The fetal shunts were obliterated. The liver weighed 325 grams and showed distinct lobulation with yellowish coloration of the pericentral zone. The respiratory system, neck organs, pancreas, gastrointestinal tract, and genitourinary system showed no gross abnormalities. Sections of heart, liver, and muscle were preserved in formalin and 95 per cent alcohol for glycogen stains. Multiple sections of the heart showed a greatly altered myocardial structure with areas of fibrous tissue. These areas were most prominent in the central portions of the papillary muscles and the perivascular and subendocardial regions. Occasional clustered or scattered leukocytes were seen without definite distribution. The remaining myocardial fibers were fragmented irregularly and varied greatly in thickness, the majority being markedly hypertrophic. Atrophic fibers were found in the neighborhood of the areas of fibrous tissue. There was a marked variation in size and staining reaction of the myocardial nuclei. Some were pyknotic and small and others were vescicular and easily mistaken for giant cells. Mytotic figures were not frequent. Perinuclear vacuolation of the myocardial fibers was as frequently found as the fibrotic process. In most places, the nucleus was centrally located and well preserved with sarcoplasm reduced to a narrow rim giving a lace-like appearance to the section. With Best's carmine, and periodic acid stains these spaces were partially filled with bright red granules. This vacuolation predominated in the subendocardial region being less frequently seen in sections of the auricular walls (Fig. 3). These areas were penetrated by normally lined capillaries. Cross striation and myofibrils of the nonvacuolated fibers were distinct. In a few areas, granular and hyaline degeneration of the sarcoplasm was seen. In these areas, the myocardium appeared as fragments of homogeneous eosino-

philic substance devoid of nuclei. A few calcium deposits were found among the degenerated myocardium. The endocardium was thickened to four times normal size, more so in the left than in the right ventricle. The elastic tissue stain failed to demonstrate an increase of elastic fibers, however, the normal elastic fibers were interrupted and had lost their allignment. The liver showed normal pattern with extensive vacuolation in the pericentral region. These vacuoles were shown to contain fat with Sudan III stain. Areas of glycogen granules were few in number. There were a few deposits

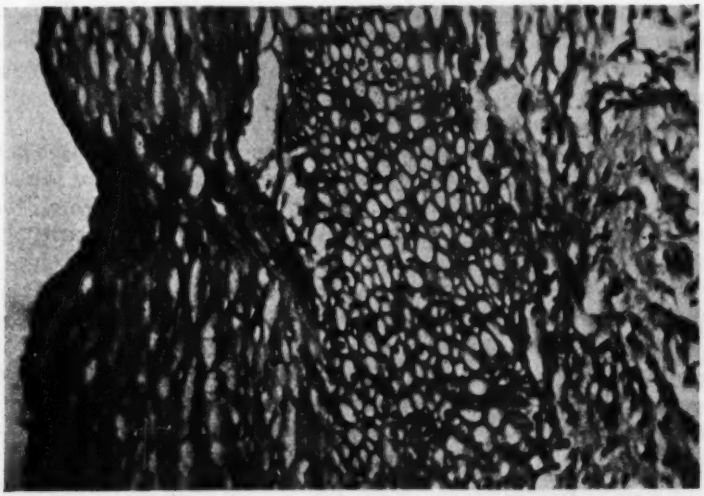


FIG. 3. Section of the left ventricle showing myocardial vacuolization of the myocardium and endocardial thickening.

of calcium in the renal cortices and in the cortical medullary junctions of the adrenals; otherwise, these organs were normal.

COMMENT

This child had frequent attacks of tonsillitis followed by weakness and pallor. He developed anemia, hypertension, albuminuria, and azotemia. The cardiomegaly, discovered before the symptoms of nephritis became evident, was progressive resulting in cardiac decompensation. The attacks of dyspnea and cyanosis were most likely acute cardiac episodes. The symptoms of nephritis improved but the remainder of the clinical picture gradually worsened. The fact that cardiomegaly appeared prior to the appearance of the nephritic picture, suggests that this heart failure was not because of

the myocarditis associated with glomerulonephritis. The occasional low blood sugar suggests the possibility of glycogen storage disease, but all laboratory findings necessary to this diagnosis including ketosis, abnormal glucose tolerance curves, insulin sensitivity, and lack of response to adrenalin were absent.

The glycogen content of the patient's heart was 1.25 per cent and the histologic appearance of many areas of glycogen, as shown by selective staining techniques, suggests the diagnosis of cardiac glycogen disease. Mowry and Bangle have demonstrated that extensive glycogen deposits occur in the hypertrophied hearts of infants under eight months of age. Thus, this finding alone is not sufficient for the diagnosis of glycogen storage disease of the heart. Subsequent studies showed that 35 per cent of the glycogen remained after twenty-four hours at room temperature which is suggestive of the fact that the glycogen is resistant to hydrolysis.

The lack of knowledge concerning the storage and fate of glycogen in the heart increases the difficulty of coming to a conclusion concerning this case. The work of Mowry and Bangle[3] indicates that besides diabetes, there seems to be no marked storage of glycogen in adult hearts, but that in a small number of infants below eight months of age, a considerable quantity of glycogen might be found. One factor might tie together the storage of glycogen in both infant hearts, adult diabetic hearts and those with glycogenosis of the liver and that is the presence of ketone acids or short chain fatty acids in the blood, since these acids were found to cause glycogen deposition in the hearts of experimental animals.[4] Although ketosis was not present in our patient from urine reports, this is no assurance that there was not a fairly high level of ketone acids in the blood. Furthermore, the presence of abnormal quantities of fatty acids in the blood could not be ruled by any examination made on our patient or made routinely on the patients of Mowry and Bangle's series. Certainly, the occurrence of glycogen storage in the heart in the hepatic form of glycogen disease is sufficiently sporadic and unrelated to the nature of the hepatic disease to suggest a secondary lapse which could well be the same as in our patient.

The finding of large amounts of glycogen in this patient's heart does not rule out the diagnosis of myocardial fibrosis since no determinations of myocardial glycogen have been made in this disease to our knowledge. The possibility that the glycogen deposition, particularly of a fairly resistant form of glycogen, occurs in those cases which have previously been diagnosed as myocardial fibrosis is enhanced by the fact that this heart resembled the gross pathological picture of myocardial fibrosis and had a similar clinical course. It may well be that chemical analysis of glycogen in cases considered to be myocardial fibrosis will reveal an identity between these cases and cardiac glycogenosis.

REFERENCES

1. Holt, E. and Bridge, L. E.: J. Pediatrics, **27:** 299, 1945.
2. Andersen, D. H., di Sant'Agnese, P. A., Mason, H. H., and Bauman, W. A.: Pediatrics, Vol. 6, Nos. 3 and 4, 1950.
3. Mowry, and Bangle: Am. J. Path. **27:** 611, 1951.
4. Lackey, R. W., Bunde, C. A., and Hanis, L. C.: Proc. Soc. Exp. Biol. and Med. **66:** 433, 1947.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.

Assisted by: Ruth Lau, M.D.

By Invitation: William Dorrance, M.D.

Ruth Lau, M.D.

This two and one-half year old white male was admitted to The Children's Hospital on August 15 in extremis. He had been well until five days prior to admission when he began to vomit several times each day. This vomiting continued for three days, then stopped spontaneously. The patient had been very restless, refused his food for two days before admission and was semi-comatose on the day of admission.

The family history was noncontributory. The child was delivered normally but was said to have had suffered a collapsed lung and some cerebral injury at birth. The latter condition was believed to be the cause of his mental retardation, as his vocabulary was limited to a few words and he had failed to walk well prior to admission.

Physical examination on August 15 revealed an acutely ill, restless and semi-comatose child with marked pallor of the skin and the mucous membranes. His temperature was 102.0 F.; pulse rate, 130; and the respiratory rate, 45 per minute. The head appeared elongated and smaller than usual. The pupils were dilated and the fundi appeared to be pale. There was no choking of the disks. The neck was supple, the chest was resonant to percussion and auscultation. The cardiac sounds were normal. The liver extended to the level of the umbilicus and was firm in consistency. The testicles were found in the inguinal regions. The extremities were flaccid and there were no pathological reflexes.

Hemogram on August 15 revealed 7 grams of hemoglobin, 2,500,000 erythrocytes, and 10,000 leukocytes with 48 per cent polymorphonuclear cells. The platelets numbered 185,000 per cubic millimeter. This examination was made after a blood transfusion. The urine was cloudy, showing 300 milligrams per 100 milliliters albumin, 3 plus acetone, and the presence of erythrocytes.

The patient was given 250 milliliters of whole blood followed by 250 milliliters of plasma intravenously. Despite the transfusion, he continued to be listless and his condition became critical. The temperature rose to 106.0 F. and the abdomen became distended. He failed to respond to any palliative treatment. The peristaltic sounds were indistinct and the superficial veins of the abdominal wall were markedly dilated. Fresh blood oozed out from the phlebotomy wound and continued to do so for more than one hour. He gradually became cyanotic and pursued a downhill course. Just

before death, which occurred twenty-five hours after admission on August 16, he vomited a large amount of dark red blood.

DISCUSSION

William Dorrance, M.D.: We have relatively few positive findings. This pertains particularly to the history and the laboratory tests. A child who becomes ill and dies in five days with no more indication of a diagnosis than we have in this case is unusual.

The initial symptom of vomiting could be caused by a myriad of things, ranging from faulty feeding or pyloric stenosis, hardly likely in our child of two and one-half years, to the nervous or habit vomiting seen in neurotic children and for which we have no background at all. Vomiting is the initial symptom in many minor and major infections. Persistent vomiting, as it occurred in that case, is found in intestinal obstruction from various causes including peritonitis, which probably produces paralytic ileus. Appendicitis, possibly ruptured, must be thought of, although in the light of later signs and symptoms, this diagnosis becomes less tenable. Organic disease of the nervous system, including infections such as meningitis and space-occupying lesions, must be considered. Finally, and, perhaps, more likely than most of the preceding, is the ingestion of a toxic substance.

The next topic in the history to be taken up is the indefinite story of a birth injury and mental and physical retardation. However, since the child was allegedly well until five days prior to admission, I doubt that this had a part in his present illness.

The physical examination is the only part of the protocol that gives us much to go on. The child was acutely ill, semicomatose, and, evidently, quite anorexic as evidenced by the pallor and later by the hemoglobin and the red blood count. He was febrile. There may have been physical deformity as shown by the oddly-shaped head. All else was essentially normal except for the enlargement of the liver. Therefore, our differential diagnosis will lie chiefly in the field of those diseases causing hepatomegaly.

The laboratory helps us very little showing only an anemia. There was no true thrombopenia, 185,000 being low normal for a platelet count and almost ruling out a disease of this sort causing the anemia. The urine showed albuminuria, acetone, and many erythrocytes. Acute glomerulonephritis must be thought of, but I do not see how this could have caused the enlargement of the liver or the sudden death accompanied by bleeding from several sources. No mention was made of hypertension or convulsions which usually accompany acute fulminating nephritis.

After admission, the child became worse and apparently had some disturbance of the clotting mechanism causing bleeding from the phlebotomy wound, the gastro-intestinal tract, and the kidneys. Our diagnosis, therefore,

lies somewhere among those diseases causing hepatomegaly. Since there was no jaundice, cirrhosis is not too likely. Although, in certain cases of biliary cirrhosis, jaundice need not be present. Furthermore, cirrhosis is not a rapidly-fatal disease such as this. Diseases of the reticuloendothelial system are more likely possibilities. One of these, Neimann-Pick's disease, occurs mainly in Jewish infants and is characterized by mental and physical retardation. The spleen, as well as the liver, enlarges; the skin may be yellowish-brown and a cherry red spot on the macula, similar to that in Tay-Sach's disease, may be seen. Anemia and fever are often present. The disease is relatively slow in its course rather than fulminating as in our case.

Gauchér's disease in the acute infantile form resembles Neimann-Pick's disease but again the spleen is enlarged as well as the liver, and the disease is progressive.

Letterer Siwe's disease may cause hepatomegaly, but it also causes splenomegaly and often a generalized lymphadenopathy neither of which are present in this case. Von Gierke's disease causes enlarged liver, retarded growth and development, and mental retardation, but it is slow in progression and is not likely to cause a bleeding tendency.

To return to something mentioned earlier, the possibility of the ingestion of some toxic substance must not be forgotten. If sufficient liver damage was caused by something of this nature, a bleeding tendency might well have been produced.

Last but not least, we must consider neoplasms. Leukemia, a generalized type of disease, usually *does* cause hepatomegaly invariably, in addition to anemia and disturbance of the clotting mechanism. Fever and prostration are commonly present but, again, even with acute leukemia the course is not often so rapid as in our case. Tumors of the liver itself must also be considered. These may be benign or malignant. We have little evidence in this case to make such a diagnosis.

In closing I will say that I frankly do not know what killed this child. I would suspect a neoplasm, either leukemia or a primary tumor of the liver, one of the reticuloendothelioses, or some ingested toxic substance causing destruction of the liver tissue.

PATHOLOGIC DISCUSSION

E. Clarence Rice, M.D. Post mortem examination revealed a well nourished and developed two and one-half year old white male whose length was 98 centimeters and whose weight was 13,440 grams. The skin was normal, no rashes, bruises, or hemangiomata being present. The abdomen was slightly distended and the liver was palpable three fingers below the right costal margin. A few dilated venules were visible over the abdomen.

The peritoneal cavity contained about 75 milliliters of clear, yellow fluid and there were no adhesions of the serous membranes.

The only organs showing pathologic changes were the lungs, liver, kidneys, intestine, and brain. The lungs grossly were slightly heavier than normal although they appeared smaller. On cut section, portions of the lung parenchyma appeared more mottled, firmer, and less crepitant than the remainder, suggesting pneumonia and atelectasis.

The liver was very large, extending 7 centimeters below the midline and the right costal margin. Its lower edge was rounded and its color was a mottled red, green, and black. The surface was smooth and tense to palpation. Aspiration of the organ revealed free flowing blood. When sectioned, the liver resembled a sponge which had been soaked in blood. The hepatic parenchyma was visible as a network of tissue forming venous lakes of various sizes. No large areas of hepatic destruction were present, however.

There were several small ecchymotic areas in the mesentery of the small bowel along with many reddened lymph nodes. A hematoma measuring 2×3 centimeters was present in the serosa of the sigmoid, but did not communicate with the mucosa or the lumen.

The right kidney was slightly larger than the left and on cut section, a hemorrhagic area was visible in the region of the renal calyces. The cortex and medulla were normal. The right ureter contained a partially organized clot in its lumen about 4 centimeters from the uretero-vesicle junction.

The surface of the right parietal area of the brain was covered with a purple clot of blood measuring 4 by 5 centimeters which was easily removed by wiping. The brain on coronal section showed only slight congestion. The cisternal fluid was grossly bloody.

Histologically, the lung revealed alveolar wall thickening with an infiltration of polymorphonuclear cells in the walls and alveolar lumina. An exudate of fibrinous and fatty material was present in the lumina of many alveoli, indicating aspiration.

Microscopic section of the liver revealed a large number of blood-filled spaces, varying in size from capillaries to large sinusoids. Many of these spaces were lined by endothelium varying from cuboidal type in the small vessels to pavement type in the large sinusoids. Many large groups of capillaries were present. There was no evidence of an abnormal hyperplasia of the endothelium lining the blood-filled spaces.

Precipitated fibrin and thin strands of fibrous tissue lined many of the blood-filled spaces. The erythrocytes in many areas had degenerated, the resulting debris having assumed an amorphous orange-colored appearance. The precipitated material had formed columns in several portions of the section, separated by fibrous tissue strands. Round cells and polymorphonuclear leukocytes had infiltrated into portions of the parenchymal tissue which was undergoing necrosis.

The hepatic cells showed the results of compression by the extravasated blood and the marked vascular engorgement. In some areas, relatively normal hepatic cells were visible but in other sections only a faint outline of the liver cells was visible, each enclosing a pyknotic nucleus. The majority of the polygonal cells had undergone vacuolization and increased granularity, although the nuclei appeared normal.

In the regions of the hepatic trinities, a marked compression and distortion of the portal venules and bile ducts had occurred.

The kidneys, histologically, revealed marked hemorrhage beneath the mucosa of the renal pelvis but the parenchyma of the kidney was uninvolved except for an occasional collection of lymphocytes and tubular epithelial degeneration.

The pathologic diagnoses were:

1. Massive hepatic hemangioma (cavernous type).
2. Hemorrhage
   A. Subarachnoid space
   B. Intestinal wall
   C. Renal pelvis
3. Atelectasis, bronchopneumonia, secondary to aspiration of foreign material.

Cause of death: Subarachnoid hemorrhage due to clotting defect secondary to hepatic insufficiency.